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Protective role of apigenin in cisplatin-induced renal injury

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ABSTRACT

This study aimed to investigate the effects and molecular mechanisms of the effects of apigenin on cisplatin (CP)-induced kidney injury in mice. Apigenin was intraperitoneally administered for 3 consecutive days before CP treatment. We found that apigenin pretreatment significantly attenuated the damage to the kidneys and decreased the levels of serum creatinine, blood urea nitrogen (BUN), glutathione peroxidase (GSH-PX) and superoxide dismutase (SOD), which were increased by CP. Apigenin significantly decreased the levels of TNF-α, IL-1β and TGFβ in the kidneys. Additionally, apigenin inhibited the activations of CYP2E1, phospho-NF-κB p65 and phospho-P38 MAPK in CP-induced renal injury. These results suggest that the renoprotective effects of apigenin may be related to the suppressions of oxidative stress and inflammation in CP-induced renal injury in mice.

Contents

1. Introduction

Cisplatin (cis-diamminedichloroplatinum (II), CP) is a potent anti-cancer drug this is widely used and highly effective against various types of tumors, including testicular, ovarian, head and

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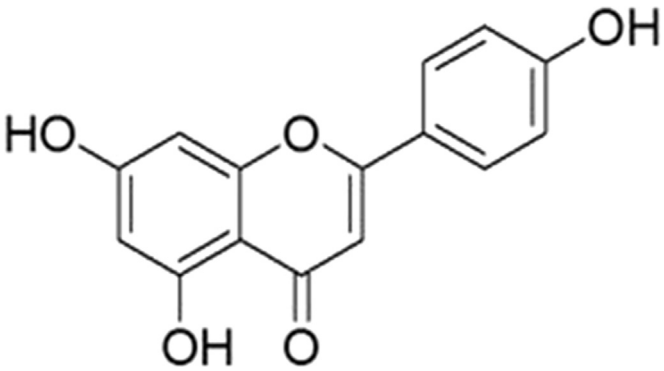

Fig. 1. The chemical structure of apigenin.

Table1
Primers used in this study.

Primer name	Nucleotide sequence (5′–3′)
TNF-α forward	ACGGGCTTTACCTCATCTACTC
TNF-α reverse	GCTCTTGATGGCAGACAGG
IL-1β forward	AGGTGGTGTCGGTCATCGT
IL-1β reverse	GCTCTCTGTCCTGGAGTTTGC
TGFβ forward	AGGGCTACCATGCCACTTC
TGFβ reverse	GCGGCACGCAGCACGGTGAT
GAPDH forward	TCAACGGGAAGCTCACTGG
GAPDH reverse	CCCCAGCATCGAAGGTAGA

neck, and bladder carcinomas (Arany and Safirstein, 2003; Osanto et al., 1992). However, the clinical use of CP is limited by its numerous side effects in normal tissues (Miller et al., 2010; Pabla and Dong, 2008). The main dose-limiting factor related to CP is nephrotoxicity. Despite its potential for cancer therapy, nephrotoxicity is observed in approximately 32–38% of patients who are treated with CP (Sanchez-Gonzalez et al., 2011; Shord et al., 2006). The pathogenesis of CP-induced nephrotoxicity has been reported to be associated with renal cell oxidative stress and inflammation (Pabla and Dong, 2008; Wei et al., 2015). The prevention of CP-induced nephrotoxicity has primarily focused on antioxidant and anti-inflammatory factors.

Apigenin (4′, 5, 7-trihydroxyflavone, $C_{15}H_{10}O_5$, molecular weight 270.24, Fig. 1) is a plant flavone that is abundantly present in a variety of fruits and vegetables, such as oranges, grapefruit, celery, parsley, onions, chamomile, and wheat sprouts (Birt et al., 2001; Patel et al., 2007). Apigenin has been reported to possess a number of biological properties, such as antioxidant, anti-inflammatory, and anti-carcinogenic effects (Nicholas et al., 2007; Tatsuta et al., 2000; Wei et al., 1990). A recent report highlighted that apigenin can ameliorate CP-induced nephrotoxicity in human renal proximal tubular epithelial cells in vitro (Ju et al., 2015). However, there is little information regarding the effects of apigenin on CP-induced renal injury in mice in vivo. The purpose of this study was to investigate the protective role of apigenin against CP-induced renal injury in mice and the mechanism of this action.

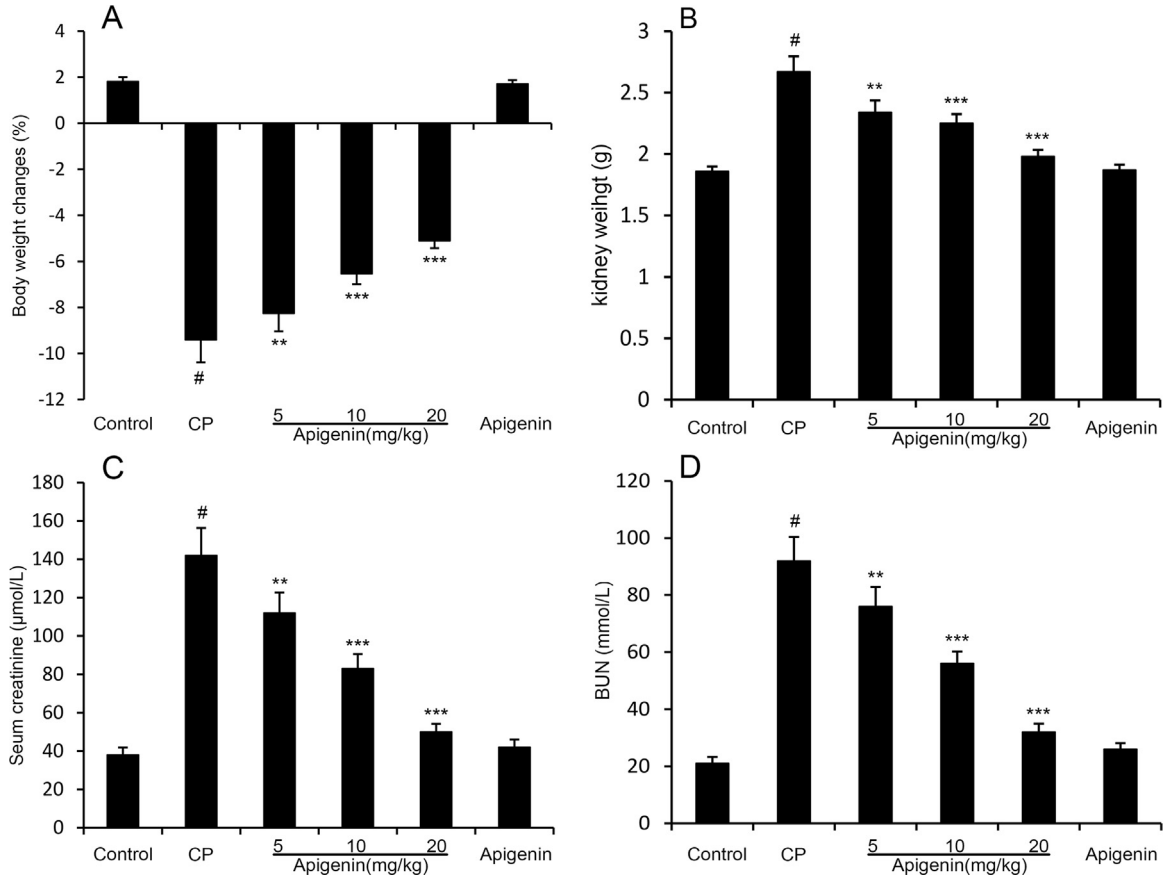

Fig. 2. Mice were given an intraperitoneal injection of apigenin respectively for 3 consecutive days before injection with cisplatin. Four days after cisplatin injection, mice were killed by cervical dislocation. (A) Body weight changes, (B) kidney weights, (C and D) the concentrations of Serum creatinine and BUN were presented in mice. Values are presented as mean ± S.E.M (n=6) of three independent experiments and differences between mean values were assessed by one-way ANOVA and Tukey's multiple comparison tests. Number sign (#) indicates $P < 0.01$ vs. control group. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ vs. CP group.

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